QR180.J6

STIC-ILL

From: Spector, Lorraine
Sent: Sunday, April 06, 2003 12:21 PM
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Subject: REFERENCE request for Serial No. 09/079834

Importance: High

Q27110

STIC,

Please send the following references:

1) Reduction of antiviral CD8 lymphocytes in vivo withdendritic cells expressing *Fas* *ligand*-increased survival of viral (lymphocytic choriomeningitis virus) central nervous system infection.
Wolfe Tom; Asseman Chrystelle; Hughes Anna; Matsue Hiroyuki; Takashima Akira; von Herrath Matthias G; et al
Division of Immune Regulation, La Jolla Institute for Allergy and Immunology, 10355 Science Center Drive, San Diego, CA 92121, USA.
Journal of immunology (Baltimore, Md. - 1950) (United States) Nov 1 2002, 169 (9) p4867-72, ISSN 0022-1767 Journal Code: 2985117R Contract/Grant No.: DK51091; DK; NIDDK; U-19AI51973; AI; NIAID; + Document type: Journal Article

2)11702788 99138821 PMID: 9973398
Induction of specific T cell tolerance by *Fas* *ligand* -expressing antigen-presenting cells.
Zhang H G; Su X; Liu D; Liu W; Yang P; Wang Z; Edwards C K; Bluethmann H; Mountz J D; Zhou T
Division of Clinical Immunology and Rheumatology, University of Alabama, Birmingham, AL 35294, USA.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Feb 1 1999, 162 (3) p1423-30, ISSN 0022-1767 Journal Code: 2985117R Contract/Grant No.: AR44982; AR; NIAMS

Thanks.

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    $0.00  Estimated cost File410
    $0.01  TELNET
    $0.01  Estimated cost this search
    $0.01  Estimated total session cost   0.234 DialUnits
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*File 155: Medline has been reloaded and accession
numbers have changed.  Please see HELP NEWS 155.

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       76035  LIGAND
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        7609  APC
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        9558  APC?
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 4/3,AB/1
DIALOG(R)File 155:MEDLINE(R)
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14617617  22173487  PMID: 12186186
 Elimination of virus-specific cytotoxic T cells in the
liver.  Dennert Gunther
 Department of Molecular Microbiology and
Immunology, USC/Norris Comprehensive Cancer Center,
Keck School of Medicine at USC, Los Angeles
90089-9176, USA. dennert@hsc.usc.edu
 Critical reviews in immunology (United States)  2002,
22 (1)  p1-11, ISSN 1040-8401  Journal Code: 8914819
 Contract/Grant No.: AI 40038; AI; NIAID; AI 43954;
AI; NIAID  Document type: Journal Article; Review;
Review, Tutorial  Languages: ENGLISH
 Main Citation Owner: NLM
 Record type: Completed
 Immune responses in the liver have been studied for
more than three decades, raising intriguing questions but
providing few definitive answers. Many observations
pertaining to immunity in this organ are unexpected and
some of them even contradictory: parenchymal cells in the
liver are readily accessible to circulating
lymphocytes and may function as antigen-presenting
cells (*APC*), yet antigens expressed in the liver often
fail to induce responses and may cause systemic
tolerance. There are rare lymphocyte classes in the liver,
yet reasons why these cells reside in this organ and why
immune responses are often poor remain to be elucidated.
Here one of the central questions in immune
responses in the liver is discussed (i.e., the ability of
the adaptive T-cell-mediated immune response to clear
a virus infection). An attempt is made to explain the
intriguing observation that non-self-antigens expressed
in the liver may induce unresponsiveness. It is shown that
cell-mediated immunity to a viral infection is terminated,
coincident with cell death of virus-specific cytotoxic
T-lymphocytes (CTL) early after infection. Death of CTL
is shown to involve interaction of Fas with *Fas*
*ligand*, pointing to fratricide between activated CTL.
The observation that T-cell death is inhibitable by
injection of interleuken-2 is interpreted to point to a
mechanism involving insufficient stimulation of T cells in
conjunction with a death signal by Fas. The hypothesis
is put forward that antigen presentation by
unconventional *APC* in the liver leads to T-cell
activation, in turn inducing lytic activity and expression
of Fas and FasL on CTL. CTL then commit fratricide,
aided by insufficient cytokine production and resulting
in clonal elimination of virus-specific T cells and induction
of tolerance.


 4/3,AB/2
DIALOG(R)File 155:MEDLINE(R)
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14522054  22482659  PMID: 12594303
 Synergistic anti-tumor responses after
administration of agonistic antibodies to CD40 and
IL-2: coordination of dendritic and CD8+ cell responses.
 Murphy William J; Welniak Lisbeth; Back Timothy;
Hixon Julie; Subleski Jeff; Seki Naoko; Wigginton Jon
M; Wilson Susan E; Blazar Bruce R; Malyguine Anatoli
M; Sayers Thomas J; Wiltrout Robert H
 Department of Microbiology, University of Nevada
School of Medicine, Reno, NV 89557, USA.
wmurphy@unr.edu
 Journal of immunology (Baltimore, Md. - 1950) (United
States)  Mar 1 2003, 170 (5)  p2727-33, ISSN
0022-1767  Journal Code: 2985117R  Contract/Grant
No.: NO1CO12400; CO; NCI; R01CA72669; CA; NCI;
R01CA95572; CA; NCI
 Document type: Journal Article
 Languages: ENGLISH
 Main Citation Owner: NLM
 Record type: In Process
 In cancer, the coordinate engagement of
professional *APC* and Ag-specific cell-mediated
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effector cells may be vital for the induction of effective antitumor responses. We speculated that the enhanced differentiation and function of dendritic cells through CD40 engagement combined with IL-2 administration to stimulate T cell expansion would act coordinately to enhance the adaptive immune response against cancer. In mice bearing orthotopic metastatic renal cell carcinoma, only the combination of an agonist Ab to CD40 and IL-2, but neither agent administered alone, induced complete regression of metastatic tumor and specific immunity to subsequent rechallenge in the majority of treated mice. The combination of anti-CD40 and IL-2 resulted in significant increases in dendritic cell and CD8(+) T cell number in advanced tumor-bearing mice compared with either agent administered singly. The antitumor effects of anti-CD40 and IL-2 were found to be dependent on CD8(+) T cells, IFN-gamma, IL-12 p40, and *Fas* *ligand*. CD40 stimulation and IL-2 may therefore be of use to promote antitumor responses in advanced metastatic cancer.

4/3,AB/3
DIALOG(R)File 155:MEDLINE(R)

14129303 22278616 PMID: 12391197
Reduction of antiviral CD8 lymphocytes in vivo with dendritic cells expressing *Fas* *ligand*-increased survival of viral (lymphocytic choriomeningitis virus) central nervous system infection.
Wolfe Tom; Asseman Chrystelle; Hughes Anna; Matsue Hiroyuki; Takashima Akira; von Herrath Matthias G; et al
Division of Immune Regulation, La Jolla Institute for Allergy and Immunology, 10355 Science Center Drive, San Diego, CA 92121, USA. Journal of immunology (Baltimore, Md. - 1950) (United States) Nov 1 2002, 169 (9) p4867-72, ISSN 0022-1767 Journal Code: 2985117R Contract/Grant No.: DK51091; DK; NIDDK; U-19AI51973; AI; NIAID; + Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In vivo administration of *APC* expressing *Fas* *ligand* (Fas-L(+) dendritic cells (DCs)) has shown promise in dampening allergic reactions and transplant rejection. Since the effect in these studies was mainly on CD4 lymphocytes, our goal was to evaluate the ability of such killer DCs to eliminate antiviral CD8 lymphocytes and in this way ameliorate viral immunopathology or, conversely, impede viral clearance. Intravenous administration of Fas-L(+) DCs resulted in a 50% reduction of lytic CD8 precursors following intracerebral infection with lymphocytic choriomeningitis virus (LCMV), and accordingly, immunopathology and survival of LCMV meningitis were improved, whereas viral clearance remained unaffected. In transfer studies the effect of the Fas-L(+) DCs was only quantifiable on experienced, not naive, CD8 lymphocytes. Importantly, loading of Fas-L(+) DCs with viral Ag before therapy was not necessary to achieve this effect, indicating that non-LCMV-infected Fas-L(+) DCs acquired viral Ag during acute LCMV infection in vivo. Our studies delineate important aspects for the clinical use of Fas-L(+) DCs in vivo. One should expect that they acquire viral Ags and suppress antiviral CD8 responses to some degree when given while an acute infection is ongoing. In terms of safety it is encouraging that resolution of the infection, at least in the case of LCMV, is not inhibited.

4/3,AB/4
DIALOG(R)File 155:MEDLINE(R)

14016797 22297653 PMID: 12409256
Effective treatment of established mouse collagen-induced arthritis by systemic administration of dendritic cells genetically modified to express FasL.
Kim Seon Hee; Kim Sunyoung; Oligino Thomas J; Robbins Paul D; et al Department of Molecular Genetics and Biochemistry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261, USA. Molecular therapy - the journal of the American Society of Gene Therapy (United States) Nov 2002, 6 (5) p584-90, ISSN 1525-0016 Journal Code: 100890581
Contract/Grant No.: AR-6-2225; AR; NIAMS; DK44935; DK; NIDDK; + Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
Previous reports have demonstrated the ability of antigen-presenting cells (*APCs*), genetically modified to express *Fas* *ligand* (FasL), to inhibit T-cell responses through the induction of apoptosis of antigen-specific T cells. Here we have examined the ability of primary mouse bone marrow-derived dendritic cells (DCs), genetically modified by adenoviral infection to express FasL, to inhibit progression of established collagen-induced arthritis (CIA) in DBA/1 mice. Systemic injection of DC/FasL into mice with established CIA resulted in substantial disease amelioration as determined by analysis of paw swelling, arthritic index, and number of arthritic paws. Moreover, a single injection of DC/FasL resulted in extended suppression of disease. We also demonstrate that treatment of arthritic mice with DC/FasL suppressed interferon-gamma (IFN-gamma) production from spleen-derived lymphocytes and reduced T-cell proliferation following collagen stimulation without affecting the levels of anti-collagen antibody isotypes. These results demonstrate that systemic administration of DC/FasL is able to suppress collagen-reactive T cells,

resulting in effective and sustained treatment of established CIA.

4/3,AB/5
DIALOG(R)File 155:MEDLINE(R)

14010431 22290529 PMID: 12403361
Specific deletion of autoreactive T cells by adenovirus-transfected, *Fas* *ligand*-producing antigen-presenting cells. Zhan Huang-Ge; Mountz John D; Fleck Martin; Zhou Tong; Hsu Hui-Chen; et al
Department of Medicine, University of Alabama at Birmingham, 35294, USA. Immunologic research (United States) 2002, 26 (1-3) p235-46, ISSN 0257-277X Journal Code: 8611087
Contract/Grant No.: N01 AR 6-2224; AR; NIAMS; R01 AG 11653; AG; NIA; R01-AI-46990; AI; NIAID; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
Immune privilege is a unique strategy developed in several internal organs that can prevent the development of immune attack against these vital organs. One critical mechanism of immune privilege is utilization of Fas/FasL-mediated apoptosis to delete the invading T cells at the immune privilege sites. In this article, we describe the development and application of a unique cell-gene therapy to correct defective FasL-mediated apoptosis and autoimmune disease in autoimmune mice. This cell-gene therapy strategy using antigen-presenting cells (*APCs*) to express FasL is not only a therapeutic tool, but also has allowed us to understand the complexity of T cell regulation and the concept of eliminating T cells in the spleen, lymph node, or elsewhere in vivo to regulate the homeostasis of the peripheral T cell response. In this regard, the FasL-expressing *APCs* can be considered as circulating and regulatable immune privilege sites. Our studies provide substantial evidence that FasL-expressing *APCs* can be introduced exogenously without liver toxicity to eliminate infiltrating T cells and prevent the development of immune attack in lung, liver, kidney, joint, and salivary gland. Therefore, given the hazardous potential of persistent T cell invasion at the local inflammatory site, it is tempting to speculate that such an endogenous control mechanism occurs normally in vivo to limit a chronic T cell inflammatory response.

4/3,AB/6
DIALOG(R)File 155:MEDLINE(R)

11953734 99397998 PMID: 10468788
Fas/*Fas* *ligand* -mediated elimination of antigen-bearing Langerhans cells in draining lymph nodes.
Kawamura T; Azuma M; Kayagaki N; Shimada S; Yagita H; Okumura K Department of Immunology, Juntendo University School of Medicine, Tokyo 113, Japan.
British journal of dermatology (ENGLAND) Aug 1999, 141 (2) p201-5, ISSN 0007-0963 Journal Code: 0004041
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Epidermal Langerhans cells (LC) are potent antigen-presenting cells (*APC*) that play a crucial part in initiating cutaneous immune responses. Although functional roles of LC as *APC* in the draining lymph node have been well investigated, little is known about the fate of LC after the antigen presentation to T cells. In this report, we demonstrate that antigen-bearing LC that migrated into the draining lymph nodes and were identified as fluorescent cells after skin painting with fluorescein isothiocyanate also expressed the Fas antigen. Clearance of the antigen-bearing LC was significantly delayed and the ratio of dead cells was reduced in Fas-deficient lpr and *Fas* *ligand* (FasL)-deficient gld mice at 2 days after skin painting, suggesting the involvement of a Fas/FasL-mediated pathway in the elimination of antigen-bearing LC in draining lymph nodes. These results suggest that a substantial population of LC after antigen presentation may undergo Fas/FasL-mediated apoptosis and that the elimination of active *APC* may be important for preventing excess immune responses.

4/3,AB/7
DIALOG(R)File 155:MEDLINE(R)

11702788 99138821 PMID: 9973398
Induction of specific T cell tolerance by *Fas* *ligand* -expressing antigen-presenting cells.
Zhang H G; Su X; Liu D; Liu W; Yang P; Wang Z; Edwards C K; Bluethmann H; Mountz J D; Zhou T
Division of Clinical Immunology and Rheumatology, University of Alabama, Birmingham, AL 35294, USA.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Feb 1 1999, 162 (3) p1423-30, ISSN 0022-1767 Journal Code: 2985117R
Contract/Grant No.: AR44982; AR; NIAMS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Autocrine interaction of Fas and *Fas* *ligand* leads to apoptosis of activated T cells, a process that is critical for the maintenance of peripheral T cell tolerance. Paracrine interactions of *Fas* *ligand*

with T cells also may play an important role in the maintenance of tolerance, as *Fas* *ligand* can create immune-privileged sites and prevent graft rejection by inducing apoptosis in T cells. We surmised that *APCs* that express *Fas* *ligand* might directly induce apoptosis of T cells during presentation of Ag to the T cells, thus inducing Ag-specific, systemic T cell tolerance. Here, we show that profound, specific T cell unresponsiveness to alloantigen was induced by treatment of H-2k mice with H-2b *APCs* that expressed *Fas* *ligand* and that profound T cell unresponsiveness specific for the H-Y Ag was induced by treatment of H-2Db/H-Y TCR transgenic female mice with H-2Db/H-Y *APCs* that expressed *Fas* *ligand*. The induction of this systemic T cell tolerance required the expression of *Fas* *ligand* on the *APCs* as well as the expression of Fas on the T cells. The tolerance was restricted to the Ag presented by the *APCs* . The rapid and profound clonal deletion of the Ag-specific, peripheral T cells mediated by the *Fas* *ligand*-expressing *APCs* contributed to the induction of tolerance. These findings demonstrate that Ag-specific T cell tolerance can be induced by *APCs* that express *Fas* *ligand* and suggest a novel function for *APCs* in the induction of T cell apoptosis. Furthermore, they indicate a novel immunointervention strategy for treatment of graft rejection and autoantigen-specific autoimmune diseases.

4/3,AB/8
DIALOG(R)File 155:MEDLINE(R)

11643581 99077580 PMID: 9862744
Perforin/*Fas*-*ligand* double deficiency is associated with macrophage expansion and severe pancreatitis.
Spielman J; Lee R K; Podack E R
Department of Microbiology and Immunology, University of Miami School of Medicine, FL 33136, USA.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Dec 15 1998, 161 (12) p7063-70, ISSN 0022-1767 Journal Code: 2985117R
Contract/Grant No.: CA39201; CA; NCI; CA57904; CA; NCI; CA59531; CA; NCI Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We report that perforin/*Fas*-*ligand* double-deficient mice die early of severe pancreatitis. Female mice, in addition, are infertile and suffer from hysterosalpingitis. Tissue destruction is accompanied by infiltration with Mac-1 (CD11b)-positive monocytes/macrophages, Mac-1-positive T cells, and expansion of CD8+ T cells. In vivo inactivation of monocytes/macrophages by carrageenan reverses disease progression and restores fertility of female mice. Perforin/*Fas*-*ligand* double-deficient CD4+ or CD8+ CTL are unable to lyse cognate-activated macrophages, and therefore are unable to mediate negative feedback regulation by lysis of *APCs* , thereby preventing further T cell activation. These studies demonstrate a novel role for perforin in homeostatic regulation of the immune response.

4/3,AB/9
DIALOG(R)File 155:MEDLINE(R)

11643194 99077193 PMID: 9862377
TNF-alpha and IFN-gamma render microglia sensitive to *Fas* *ligand* -induced apoptosis by induction of Fas expression and down-regulation of Bcl-2 and Bcl-xL.
Spanaus K S; Schlapbach R; Fontana A
Department of Internal Medicine, University Hospital Zurich, Switzerland. European journal of immunology (GERMANY) Dec 1998, 28 (12) p4398-408 , ISSN 0014-2980 Journal Code: 1273201
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The immune response in the central nervous system (CNS) involves microglial cells which represent intraparenchymal antigen-presenting cells (*APC*). To control immune effector mechanisms it may be required to induce apoptosis of *APC* and thereby limit reactivation of T cells that have invaded the CNS. In the present study we investigated the susceptibility of primary murine microglia and of the murine microglial cell line BV-2 to undergo Fas-mediated apoptosis. Whereas resting microglia are resistant to *Fas* *ligand* (FasL) treatment, induction of FasL-mediated apoptosis was achieved by treatment with TNF-alpha or IFN-gamma. The effect of these cytokines was paralleled by up-regulation of Fas expression and down-regulation of Bcl-2 and Bcl-xL but not Bax. Activation of microglia by TNF-alpha and IFN-gamma was also accompanied by increased amounts of mRNA for the apoptosis inhibitor FLIP, an effect which did not protect the cells from FasL-induced apoptosis. The FasL-induced cell death pathway in microglia involves reactive oxygen intermediates because the antioxidants N-acetylcysteine and glutathione interfere with induction of apoptosis. Surprisingly, microglia constitutively express FasL on the cell surface. However, blocking of endogenous Fas-FasL interaction with Fas-Fc fusion protein did not enhance the survival of microglia, excluding the possibility of suicide or fratricide mechanisms. By their expression of FasL and their TNF-alpha/IFN-gamma-dependent sensitivity to the pro-apoptotic effect of exogenous FasL, microglial cells may influence the course of T cell-mediated diseases of

the CNS.

4/3,AB/10
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11613857 99046896 PMID: 9831033
Induction of specific T-cell tolerance by adenovirus-transfected, *Fas* *ligand*-producing antigen presenting cells. Zhang H G; Liu D; Heike Y; Yang P; Wang Z; Wang X; Curiel D T; Zhou T; Mountz J D
The University of Alabama at Birmingham, Department of Medicine, 35294, USA.
Nature biotechnology (UNITED STATES) Nov 1998, 16 (11) p1045-9, ISSN 1087-0156 Journal Code: 9604648
Contract/Grant No.: NO1-AR-6-2224; AR; NIAMS; RO1-AR-42547; AR; NIAMS Comment in Nat Biotechnol. 1998 Nov;16(11) 1011-2; Comment in PMID 9831025
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A major problem associated with adenovirus gene therapy is the T cell-mediated immune response, which is elicited by inoculation of the adenovirus vector and leads to rapid clearance of the virus and loss of transgene expression. In this study, the immune response to adenovirus was prevented by induction of specific T-cell tolerance by pretreatment with adenovirus-infected antigen-presenting cells (*APC*) that express *Fas* *ligand* . Compared with control-treated mice, the tolerized mice showed prolonged expression of lacZ upon administration of AdCMVlacZ 1 week after tolerance induction. In contrast to the control mice, the tolerized mice did not display proliferation of CD3+ T cells in the spleen in response to AdCMVlacZ. Tolerance induction also was indicated by the lower production of interferon-gamma and interleukin-2 by peripheral T cells isolated from AdCMVlacZ-challenged tolerized mice than by AdCMVlacZ-challenged control-treated mice. The T-cell tolerance was specific for the adenovirus as the T-cell responses to irrelative murine cytomegalovirus remained unimpaired. Our results indicate that adenovirus-specific T-cell tolerance can be induced by *APCs* that coexpress *Fas* *ligand* and adenovirus antigens. We propose that this new strategy can be used to induce tolerance to adenovirus vector gene therapy with resultant prolonged expression of the transgene.

4/3,AB/11
DIALOG(R)File 155:MEDLINE(R)
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11485792 98369815 PMID: 9704192
The immunology of corneal graft rejection.
Rocha G; Deschenes J; Rowsey J J
Department of Ophthalmology, Hospital San Jose de Monterrey-ITESM, Mexico.
Critical reviews in immunology (UNITED STATES) 1998, 18 (4) p305-25, ISSN 1040-8401 Journal Code: 8914819
Document type: Journal Article; Review; Review, Academic Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Corneal transplantation is the most successful of organ transplants due to the fact that the eye is an immunologically privileged site, and the cornea is an immunologically privileged tissue. The factors responsible for this include presence of the blood-aqueous barrier, the avascularity of the cornea, the absence of classic antigen-presenting cells (*APCs*) in the central cornea, inhibitory factors in the aqueous humor, the phenomenon known as anterior chamber-associated immune deviation (ACAID), and the intraocular expression of *Fas* *ligand*. Loss of ocular immune privilege can occur with breaching of the blood-ocular barrier, corneal neovascularization, migration of classic *APCs* to the center of the cornea, loss of inhibitory factors in aqueous humor, abrogation of ACAID, and loss of *Fas* *ligand* expression within the anterior chamber. The purpose of this review is to analyze these events and how they relate to corneal graft rejection. A discussion on future research and therapeutic modalities is provided.

4/3,AB/12
DIALOG(R)File 155:MEDLINE(R)
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11353326 98233672 PMID: 9574528
Ultraviolet light-induced immune tolerance is mediated via the Fas/ *Fas*-*ligand* system.
Schwarz A; Grabbe S; Grosse-Heitmeyer K; Roters B; Riemann H; Luger T A; Trinchieri G; Schwarz T
Ludwig Boltzmann Institute for Cell Biology and Immunobiology of the Skin, Department of Dermatology, University Munster, Germany. Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) May 1 1998, 160 (9) p4262-70, ISSN 0022-1767 Journal Code: 2985117R Contract/Grant No.: CA 10815; CA; NCI; CA 20833; CA; NCI; CA 32898; CA; NCI; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Hapten sensitization through UV-exposed skin induces tolerance that is mediated via the induction of hapten-specific T suppressor cells. However, the detailed mechanisms underlying tolerance induction remain unclear to date. We show here that the apoptosis-related surface Ag Fas (APO-1, CD95) and its ligand, *Fas*

ligand (FasL) are critically involved, since Fas-deficient lpr mice and FasL-deficient gld mice do not develop UV-induced tolerance. Adoptive transfer experiments revealed that the mediation of tolerance does not require the expression of Fas or FasL by the T suppressor cells but does require the expression of both molecules by the cells of mice receiving the T suppressor cells. To identify the mechanisms involved, the effect of suppressor cells on Ag-presenting dendritic cells (DC) was studied. Coincubation of hapten-pulsed DC with T cells that were obtained from UV-tolerized mice resulted in an enhanced death rate of DC, and this cell death was dependent upon Fas expression. The addition of IL-12, which recently was found to break established tolerance in vivo, prevented DC death. Moreover, IL-12 did not only rescue DC from T suppressor cell-induced death but also from apoptosis induced by rFasL, suggesting that IL-12 may interfere with the Fas/FasL system. Together, these data indicate a crucial role for the Fas/FasL system in UV-induced tolerance, and suggest that UV-induced T suppressor cells may act by inducing the cell death of *APCs* via the Fas pathway. The ability of IL-12 to break established tolerance may be due to the prevention of DC death induced by T suppressor cells.

4/3,AB/13
DIALOG(R)File 155:MEDLINE(R)

10937180 97289559 PMID: 9144464
Class I- and class II-reactive TCRs coexpressed on CD4+ T cells both trigger CD4/CD8-shared and CD4-unique functions.
Asnagli H; Schmitt-Verhulst A M; Guimezanes A
Center for Immunology, INSERM-CNRS of Marseille-Luminy, France.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) May 15 1997, 158 (10) p4533-42, ISSN 0022-1767 Journal Code: 2985117R Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
CD4+ and CD8+ T cells emerge from thymic selection expressing a TCR restricted by MHC class II (TCRII) and MHC class I (TCRI), and upon Ag stimulation develop respectively into Th and CTL effector cells. The influence of thymic differentiation and antigenic stimulation on the determination of T cell functions was studied, with CD4+ T cells expressing a transgenic TCRI that reacts with the class I alloantigen H-2K(b) in a CD8-independent fashion. Such T cells additionally express a TCR, probably TCRII, in which the transgenic TCR beta-chain is associated with endogenously rearranged TCR alpha-chains. Upon in vitro stimulation with H-2K(b)-expressing cells, both CD8+ and CD4+ transgenic TCR+ T cells developed into CTL capable of killing Ag-expressing target cells through a perforin-dependent mechanism, and secreted IL-2 and IFN-gamma. *Fas* *ligand* -dependent killing could also be induced in both CD8+ and CD4+ in vitro stimulated T cells. The capacity to secrete IL-4 was restricted to the CD4+ T cells, however, suggesting that both CD8/CD4-shared and CD4-unique programs can be elicited by stimulation of CD4 T cells through a TCRI. Acquisition of CTL function was also induced upon class II alloantigen stimulation through the endogenously rearranged TCRII, which represents a polyclonal set of TCRs. IL-2, IFN-gamma, and after restimulation, IL-4, were also produced. Thus: 1) events associated with intrathymic selection influence the gene program activated in response to the same TCRI/*APC* interaction; and 2) CD4+ T cells expressing a TCRI and a TCRII can activate the same gene program after engagement of either one of these TCRs.

4/3,AB/14
DIALOG(R)File 155:MEDLINE(R)

10888889 97240749 PMID: 9120262
Dissociation of T cell anergy from apoptosis by blockade of Fas/Apo-1 (CD95) signaling.
Hargreaves R G; Borthwick N J; Montani M S; Piccolella E; Carmichael P; Lechler R I; Akbar A N; Lombardi G
Department of Immunology, Royal Postgraduate Medical School, Hammersmith Hospital, London, United Kingdom.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Apr 1 1997, 158 (7) p3099-107, ISSN 0022-1767 Journal Code: 2985117R
Contract/Grant No.: CA60181; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Induction of anergy and deletion due to apoptosis are two of the mechanisms involved in peripheral tolerance. To clarify the relationship between these two phenomena we have used an in vitro system of T cell Ag presentation. The recognition of Ag displayed by MHC class II-expressing T cells (T-*APC*) induces partial signals in Ag-specific T cell clones. This leads to a blunted intracellular calcium flux, and the T cells become unable to proliferate in response to further challenge with professional *APC*. These T cells are unable to produce IL-2, but retain the ability to release IL-4. In the present study, we report that for some T cell clones, the predominant outcome of Ag recognition on T cells is cell death. For susceptible T cell clones, the number of cells that die is proportional to the peptide concentration. This cell death resulted from Fas/Apo-1 (CD95)/*Fas*-*ligand* interactions between the T cells, in that *Fas* *ligand* expression was detected following overnight culture of T cells with T-*APC* and

neutralizing anti-CD95 Ab protected from death. Most notably, following anti-CD95-mediated protection from apoptosis, the rescued T cells remained unable to respond to rechallenge with Ag-pulsed, professional *APC*. These data suggest that anergy and apoptosis can be separated as consequences of partial T cell signaling.

4/3,AB/15
DIALOG(R)File 155:MEDLINE(R)

10449433 96256142 PMID: 8675213
Effects of antigen presentation on superantigen-induced apoptosis mediated by Fas/*Fas* *ligand* interactions in human T cells. Boshell M; McLeod J; Walker L; Hall N; Patel Y; Sansom D Bath Institute for Rheumatic Diseases, University of Bath, UK.
Immunology (ENGLAND) Apr 1996, 87 (4) p586-92, ISSN 0019-2805 Journal Code: 0374672
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Stimulation of T cells with bacterial superantigens has several distinct functional outcomes including proliferation, anergy and apoptosis. At present however, the mechanisms that dictate whether activation, anergy, or apoptosis predominate are unclear. In this study we have investigated the effects of superantigen presentation to mature superantigen-reactive human T-cell lines. Despite expressing major histocompatibility complex (MHC) class II molecules, these lines failed to proliferate in response to superantigen in the absence of antigen-presenting cells (*APC*) but proliferated when minimal *APC* were added. In the absence of *APC* a significant proportion of the T cells underwent apoptosis. This response was rapid, antigen dependent and largely abolished by the addition of cyclosporin A. Interestingly the response was not blocked by the addition of a number of antibodies to cell surface molecules including MHC class II and intracellular adhesion molecule-1. Using both a bioassay and messenger RNA analysis we were able to demonstrate that stimulation of these T cells with superantigen resulted in the induction of *Fas*-*ligand* expression on the T cells and furthermore, the ability of these cells to induce apoptosis was inhibited by the addition of blocking Fas antibodies as well as a Fas-Fc fusion protein. These data demonstrate that stimulation of T cells with staphylococcal enterotoxin B induces expression of *Fas*-*ligand* resulting in T-cell apoptosis; however, the final outcome of proliferation or apoptosis is determined by the presence of *APC*.

4/3,AB/16
DIALOG(R)File 155:MEDLINE(R)

10235870 96037183 PMID: 7493761
Mechanism and biological significance of CD4-mediated cytotoxicity. Hahn S; Gehri R; Erb P
Institute for Medical Microbiology, University of Basel, Switzerland. Immunological reviews (DENMARK) Aug 1995, 146 p57-79, ISSN 0105-2896 Journal Code: 7702118
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
It is now well established that CD4+ T cells can express cytotoxic activity. This type of cell-mediated cytotoxicity is associated with the Th1-, but not with the Th2-phenotype. While the activation of CD4+ CTL is MHC class II-restricted, the effector phase, i.e. the target cell killing is unrestricted and antigen non-specific. In analogy to CD8+ CTL, CD4-mediated target cell death is by DNA fragmentation. However, the molecular mechanism of killing differs from CD8-mediated lysis. Thus, CD4+ CTL preferentially lyse their targets via Fas-*Fas* *ligand* interaction, whereas the major cytotoxic effect of CD8+ CTL is by granule exocytosis, i.e. perforin and granzymes. Although CD8+ CTL can also express the FasL, their lytic activity through interaction with Fas is of less importance. Likewise, some CD4+ CTL may also kill by perforin/granzymes activity, but this pathway is of minor significance. The aims of CD8- or CD4-mediated lysis are also different. Thus, the major task of CD8+ CTL which recognize and kill their targets in the context of MHC class I molecules, is the lysis of virally infected cells and battling against tumor cells. CD4+ CTL, on the other hand, have an immunomodulatory role. Thus, they preferentially eliminate activated MHC class II-positive cells, i.e. *APC*, be they monocytes/macrophages, B cells or T cells. They may lyse these cells in order to prevent an overreaction of the ongoing immune response or in order to remove potentially hazardous cells upon completion of the immune response. The Fas-FasL pathway is particularly suitable for this task as myeloid or lymphoid cells express Fas only if activated, while FasL is preferentially expressed on activated CD4+ Th1 cells. Moreover, activated T cells eliminate themselves by the Fas-mediated pathway. Whether this happens by fratricide only, or also by suicide or both is open. Moreover, CD4+ CTL are particularly suitable for killing tumor cells as well, as they are efficient effectors in bystander lysis in contrast to CD8+ CTL. On the other hand, the non-specific killing via Fas-FasL interaction, which is an important reason for the bystander lysis, may have unwanted effects in that cells which should not be eliminated could be killed. Such reactions affecting various organs and cells, e.g. the liver, thyroid or islet cells of the pancreas could be an explanation for certain

autoimmune diseases.

4/3,AB/17
DIALOG(R)File 155:MEDLINE(R)
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10030764 21966236 PMID: 11970984
Aberrant expression of *Fas* *ligand* in mice deficient for the MHC class II transactivator.
Gourley Tania S; Patel Dipak R; Nickerson Kevin; Hong Soon-Cheol; Chang Cheong-Hee
Department of Microbiology and Immunology, University of Michigan Medical School, Ann Arbor, MI 48109, USA.
Journal of immunology (Baltimore, Md. - 1950) (United States) May 1 2002, 168 (9) p4414-9, ISSN 0022-1767 Journal Code: 2985117R Contract/Grant No.: 5-T32-GM07544; GM; NIGMS; AI41510; AI; NIAID; DE13988 ; DE; NIDCR
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The MHC class II transactivator (CIITA) is a critical regulator of MHC class II genes and other genes involved in the Ag presentation pathway. CIITA-deficient mice lack MHC class II expression on almost all *APCs*. In this study, we show that these mice also have aberrant *Fas* *ligand* expression on both CD4 T cells and B cells. We found that *Fas* *ligand* expression was greatly increased on CIITA-deficient CD4 T cells during the Th1 differentiation process. However, both CIITA-deficient and control Th1 effector cells up-regulated *Fas* *ligand* to similar levels if cells were reactivated. The introduction of CIITA into primary CD4 T cells via retroviral infection resulted in a reduction in the level of *Fas* *ligand* and delay in apoptosis after activation. Interestingly, activated B cells from the CIITA-deficient mice also showed increased levels of *Fas* *ligand* that could be to some degree inhibited by the introduction of IL-4.

4/3,AB/18
DIALOG(R)File 155:MEDLINE(R)
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10006406 21935531 PMID: 11937577
Depletion of collagen II-reactive T cells and blocking of B cell activation prevents collagen II-induced arthritis in DBA/1j mice. Zhang Huang-Ge; Yang PingAr; Xie Jinfu; Liu Zhongyu; Liu Di; Xiu Liang; Zhou Tong; Wang Yongming; Hsu Hui-Chen; Mountz John D
University of Alabama, Birmingham, AL 35294, USA. Huang-Ge.Zhang@cc.uab.edu
Journal of immunology (Baltimore, Md. - 1950) (United States) Apr 15 2002, 168 (8) p4164-72, ISSN 0022-1767 Journal Code: 2985117R Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Collagen II (CII)-induced arthritis in DBA/1j mice is mediated by both CII-reactive T cells and anti-CII Ab-producing B cells. To determine the relative role of these processes in the development of arthritis, we specifically eliminated CII-reactive T cells by treating the mice with CII-pulsed syngeneic macrophages that had been transfected with a binary adenovirus system. These macrophages express murine *Fas* *ligand* in a doxycycline-inducible manner with autocrine suicide inhibited by concomitant expression of p35. The mice were treated i.v. with four doses of CII-*APC* -AdFasLp35Tet or a single dose of AdCMVsTACI (5 x 10(9) PFU), or both simultaneously, beginning 2 wk after priming with CII in CFA. Treatment with CII-*APC* -AdFasLp35Tet alone or in combination with a single dose of AdCMVsTACI prevented the development of CII-induced arthritis and T cell infiltration in the joint. The elimination of T cells was specific in that a normal T cell response was observed on stimulation with OVA after treatment with CII-*APC*-AdFasLp35Tet. Treatment with AdCMVsTACI alone prevented production of detectable levels of circulating anti-CII autoantibodies and reduced the severity of arthritis but did not prevent its development. These results indicate that the CII-reactive T cells play a crucial role in the development of CII-induced arthritis and that the anti-CII Abs act to enhance the development of CII-induced arthritis.

4/3,AB/19
DIALOG(R)File 155:MEDLINE(R)
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09936108 21848229 PMID: 11859102
Defective *Fas* *ligand* expression and activation-induced cell death in the absence of IL-2-inducible T cell kinase.
Miller Andrew T; Berg Leslie J
Department of Pathology, Program in Immunology and Virology, University of Massachusetts Medical Center, 55 Lake Avenue North, Worcester, MA 01655, USA.
Journal of immunology (Baltimore, Md. - 1950) (United States) Mar 1 2002, 168 (5) p2163-72, ISSN 0022-1767 Journal Code: 2985117R Contract/Grant No.: AI 07439; AI; NIAID; AI 37484; AI; NIAID
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The Tec family tyrosine kinase, IL-2-inducible T cell kinase (Itk), plays an important role in TCR signaling. Studies of T cells from Itk-deficient mice have demonstrated that Itk is critical for the activation

of phospholipase-Cgamma1, leading to calcium mobilization in response to TCR stimulation. This biochemical defect results in reduced IL-2 production by Itk-deficient T cells. To further characterize the downstream effects of the Itk deficiency, we crossed Itk-/- mice to a TCR-transgenic line and examined T cell responses to stimulation by peptide plus *APC*. These studies show that Itk is required for maximal activation of early growth responses 2 and 3 and *Fas* *ligand* transcription after TCR stimulation. These transcriptional defects lead to reduced activation-induced cell death of stimulated Itk-/- T cells, both in vitro and in vivo. Together these studies define an important role for Itk in TCR signaling, leading to cytokine gene expression and activation-induced cell death.

4/3,AB/20
DIALOG(R)File 155:MEDLINE(R)

09726459 21521847 PMID: 11665751
Immune reaction to breast cancer: for better or for worse? Ogmundsdottir H M
Molecular and Cell Biology Research Laboratory, Icelandic Cancer Society, Reykjavik. helgam@krabb.is
Archivum immunologiae et therapiae experimentalis (Poland) 2001, 49 Suppl 2 pS75-81, ISSN 0004-069X Journal Code: 0114365
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The infiltration of breast carcinomas with lymphoid cells has often been interpreted as an indication of an active immune response against the tumour and, thus, a favourable prognostic sign. Several studies have, however, cast doubt on this assumption. In situ breast carcinomas are more common than invasive cancers, and it may be speculated that immune surveillance plays a role in preventing some localized cancers from becoming invasive. A secondary type of immune surveillance might be implicated in the long persistence of dormant breast carcinoma cells in the bone marrow. Breast cancer cells can carry tumor-associated antigens, particularly MUC1. These may elicit specific antibody responses, but there is less evidence for a cytotoxic T lymphocyte (CTL) response. There are indications that professional antigen-presenting cells (*APC*) may be present and active at the edges of breast tumours. Breast cancer cells may also interact directly with macrophages and natural killer (NK) cells. In terms of immune effector mechanisms in breast cancer, the communication with potential effector cells is likely to be often faulty because of altered expression of HLA class I molecules. Pleiotrophic cytokines are frequently present and could have a variety of effects ranging from growth inhibition to stimulated proliferation, loss of cell adhesion and activation of matrix-degrading enzymes. *Fas* *ligand* is unlikely to play a role in the immune evasion of breast cancer. There is thus evidence for a variety of immune reactions to breast cancer. It is possible that they mediate some form of surveillance, but growing, invasive tumours have escape routes and may even use cytokines to their advantage.

4/3,AB/21
DIALOG(R)File 155:MEDLINE(R)

09684459 21476375 PMID: 11592380
Defective *Fas* *ligand* -mediated apoptosis predisposes to development of a chronic erosive arthritis subsequent to Mycoplasma pulmonis infection.
Hsu H C; Zhang H G; Song G G; Xie J; Liu D; Yang P A; Fleck M; Wintersberger W; Zhou T; Edwards C K; Mountz J D
The University of Alabama at Birmingham, 35294-0007, USA. Arthritis and rheumatism (United States) Sep 2001, 44 (9) p2146-59, ISSN 0004-3591 Journal Code: 0370605
Contract/Grant No.: N01-AR-62224; AR; NIAMS; R01-AG-11653; AG; NIA; R01-AI-46990; AI; NIAID
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
OBJECTIVE: To determine whether defective T cell apoptosis is associated with the development of a chronic arthritis subsequent to mycoplasma infection, and to determine whether deletion of T cells can prevent the development of this arthritis. METHODS: B6 wild-type (B6-+/+), B6-lpr/lpr, and B6-gld/gld mice were infected with Mycoplasma pulmonis. The severity of lymphocytic infiltration and joint damage was evaluated, and the degree of recovery of viable mycoplasma from the spleen and joints was determined. Antigen-presenting cells derived from Fas mutant lpr mice (lpr-*APC*) were transfected ex vivo with an adenovirus (Ad) vector to yield lpr- *APC* expressing high levels of *Fas* *ligand* (lpr-*APC* -AdFasL), which in turn were transferred intraperitoneally into M pulmonis-infected B6-gld/gld mice. The development of arthritis subsequent to M pulmonis infection and the induction of apoptosis of cells within the synovial tissue and lymph nodes of lpr-*APC*-AdFasL-treated B6-gld/gld mice were determined. RESULTS: Infection of B6-lpr/lpr and B6-gld/gld mice with M pulmonis resulted in an acute-phase inflammation of the synovium that later developed into a chronic erosive arthritis. Similar infection of B6-+/+ mice resulted only in an acute joint inflammatory response that resolved. Chronic arthritis in B6-gld/gld mice and B6-lpr/lpr was not due to persistent infection, since there were no differences in

the rates of clearance of M pulmonis from the joints of B6-gld/gld or B6-lpr/lpr mice compared with B6-+/+ mice. Treatment of infected B6-gld/gld mice with lpr-*APC*-AdFasL resulted in a significantly decreased incidence of chronic arthritis that was associated with a decrease in lymph node T cells, but not with apoptosis of synovial T cells or fibroblasts. CONCLUSION: Defective Fas/FasL-mediated apoptosis of T cells is an important factor that rendered arthritis-resistant B6 mice susceptible to the development of a chronic erosive arthritis subsequent to mycoplasma infection. In vivo lpr-*APC* -AdFasL cell-gene therapy is a safe and effective method for inhibiting the development of this arthritis.

4/3,AB/22
DIALOG(R)File 155:MEDLINE(R)
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09553180 21334397 PMID: 11441119
Lipopolysaccharide-activated B cells down-regulate Th1 immunity and prevent autoimmune diabetes in nonobese diabetic mice.
Tian J; Zekzer D; Hanssen L; Lu Y; Olcott A; Kaufman D L Department of Molecular and Medical Pharmacology, University of California School of Medicine, 10833 Le Conte Avenue, Los Angeles, CA 90095, USA. jtian@mednet.ucla.edu
Journal of immunology (Baltimore, Md. - 1950) (United States) Jul 15 2001, 167 (2) p1081-9, ISSN 0022-1767 Journal Code: 2985117R Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
B cells can serve dual roles in modulating T cell immunity through their potent capacity to present Ag and induce regulatory tolerance. Although B cells are necessary components for the initiation of spontaneous T cell autoimmunity to beta cell Ags in nonobese diabetic (NOD) mice, the role of activated B cells in the autoimmune process is poorly understood. In this study, we show that LPS-activated B cells, but not control B cells, express *Fas* *ligand* and secrete TGF-beta. Coincubation of diabetogenic T cells with activated B cells in vitro leads to the apoptosis of both T and B lymphocytes. Transfusion of activated B cells, but not control B cells, into prediabetic NOD mice inhibited spontaneous Th1 autoimmunity, but did not promote Th2 responses to beta cell autoantigens. Furthermore, this treatment induced mononuclear cell apoptosis predominantly in the spleen and temporarily impaired the activity of *APCs* . Cotransfer of activated B cells with diabetogenic splenic T cells prevented the adoptive transfer of type I diabetes mellitus (T1DM) to NOD/scid mice. Importantly, whereas 90% of NOD mice treated with control B cells developed T1DM within 27 wk, <20% of the NOD mice treated with activated B cells became hyperglycemic up to 1 year of age. Our data suggest that activated B cells can down-regulate pathogenic Th1 immunity through triggering the apoptosis of Th1 cells and/or inhibition of *APC* activity by the secretion of TGF-beta. These findings provide new insights into T-B cell interactions and may aid in the design of new therapies for human T1DM.

4/3,AB/23
DIALOG(R)File 155:MEDLINE(R)
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09551722 21332898 PMID: 11439154
Decreased T cell stimulatory capacity of monocyte-derived human macrophages following herpes simplex virus type 1 infection. Hoves S; Niller H H; Krause S W; Straub R; Gluck T; Mountz J D; Scholmerich J; Fleck M
Department of Internal Medicine I, The University of Regensburg, 93042 Regensburg, Germany.
Scandinavian journal of immunology (England) Jul-Aug 2001, 54 (1-2) p93-9, ISSN 0300-9475 Journal Code: 0323767
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Macrophages play a central role in establishing a specific immune response by acting as professional antigen presenting cells (*APC*) for T cells leading to a vigorous immune response. In order to analyze if Herpes simplex Virus (HSV) type 1 infection might affect the macrophage *APC* -function, monocyte-derived human macrophages were infected with HSV-1 strain F in vitro. Cocultures with allogeneic T cells revealed a strongly impaired stimulatory capacity of HSV-infected macrophages compared to uninfected controls which was not owing to a productive viral infection in macrophages. An increased expression of *Fas* *ligand* (FasL/CD95L) was detected in HSV-infected macrophages by FACS analysis. Although the majority of the macrophages expressed high levels of Fas (CD95/Apo-1), the HSV-induced upregulation of FasL did not result in an increased autocrine apoptosis of macrophages which might be related to endogenous expression of the apoptosis inhibitor FLICE inhibitory protein (FLIP). However, substantial apoptosis occurred in peripheral T cells as well as Fas-sensitive Jurkat T cells when cocultured with HSV-infected macrophages. These findings suggest that the paracrine killing of activated T cells by FasL expressing *APC* might be a novel strategy of immune evasion by HSV.

4/3,AB/24
DIALOG(R)File 155:MEDLINE(R)
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09458922 21231540 PMID: 11333146
Specific immunotherapy of experimental myasthenia gravis in vitro: the "guided missile" strategy.
Wu J M; Wu B; Miagkov A; Adams R N; Drachman D B
Neuromuscular Research Laboratory, Johns Hopkins School of Medicine, Baltimore, Maryland, 21287-7519, USA.
Cellular immunology (United States) Mar 15 2001, 208 (2) p137-47, ISSN 0008-8749 Journal Code: 1246405
Contract/Grant No.: 1-RO1NS37205; NS; NINDS; NS07368; NS; NINDS Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We describe a strategy for specific immunotherapy of myasthenia gravis (MG) based on genetic engineering of antigen presenting cells (*APCs*) to present the autoantigen acetylcholine receptor (AChR) and express the "warhead" *Fas* *ligand* (FasL). For transduction of *APCs* we prepared recombinant attenuated vaccinia virus vectors carrying the following three gene constructs: (i) AChR fused to LAMP1 to present AChR and target AChR-specific T cells; (ii) FasL to eliminate the targeted T cells; and (iii) truncated FADD to protect *APCs* from self-destruction by FasL. The engineered *APCs* effectively expressed the genes of interest and killed AChR-specific T cells in culture by the Fas/FasL pathway. T cells specific for an unrelated antigen were spared. Our in vitro demonstration that engineered *APCs* target and kill antigen-specific T cells represents a promising novel strategy for specific immunotherapy of MG and other autoimmune diseases. Copyright 2001 Academic Press.

4/3,AB/25
DIALOG(R)File 155:MEDLINE(R)

09389481 21154084 PMID: 11254740
Specific immunotherapy by genetically engineered *APCs*: the "guided missile" strategy.
Wu B; Wu J M; Miagkov A; Adams R N; Levitsky H I; Drachman D B Neuromuscular Research Laboratory, Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD 21287, USA.
Journal of immunology (Baltimore, Md. - 1950) (United States) Apr 1 2001, 166 (7) p4773-9, ISSN 0022-1767 Journal Code: 2985117R Contract/Grant No.: 1R01NS37205; NS; NINDS; NS07368; NS; NINDS Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We tested the hypothesis that *APCs* genetically engineered to present an Ag and to express *Fas* *ligand* (FasL) simultaneously can target and eliminate Ag-specific T cells. Transgenic T cells specific for influenza hemagglutinin (HA) were used as targets. We prepared recombinant vaccinia virus vectors (VVV) to transfer the gene constructs individually or simultaneously into *APCs*. We prevented unwanted viral replication by attenuating the VVVs with psoralen-UV light treatment. For presentation of the HA Ag, *APCs* were transduced with cDNA for HA flanked by sequences of the lysosome-associated membrane protein that direct efficient processing and presentation of the Ag by *APCs*. As a "warhead" for the *APCs*, we transduced them with the gene for FasL, which induces apoptosis of Fas-expressing activated T cells. To protect the transduced *APCs* from self-destruction by FasL, we transferred cDNA for a truncated form of Fas-associated death domain, which inhibits Fas-mediated cell death. Our results show that the engineered *APCs* effectively expressed the genes of interest. *APCs* transduced with VVV carrying all three gene constructs specifically killed HA-transgenic T cells in culture. Coculture with T cells specific for an unrelated Ag (OVA) had no significant effect. Our in vitro findings show that *APCs* can be genetically engineered to target and kill Ag-specific T cells and represent a promising novel strategy for the specific treatment of autoimmune diseases.

4/3,AB/26
DIALOG(R)File 155:MEDLINE(R)

09249070 20562814 PMID: 11108936
VIP and PACAP inhibit *Fas* *ligand*-mediated bystander lysis by CD4(+) T cells.
Delgado M; Ganea D
Department of Biological Sciences, Rutgers University, Newark, NJ 07102, USA.
Journal of neuroimmunology (NETHERLANDS) Jan 1 2001, 112 (1-2) p78-88, ISSN 0165-5728 Journal Code: 8109498
Contract/Grant No.: AI041786-01; AI; NIAID
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
FasL/Fas-mediated lysis represents the major cytotoxic mechanism for CD4(+) effectors, with important consequences for immune cell homeostasis. Upon stimulation by specific antigen-presenting cells (*APCs*), CD4(+) effectors can lyse the cognate *APCs* (direct targets) and neighboring innocent bystanders. Previously we showed that the neuropeptides VIP and PACAP prevent FasL expression and activation-induced cell death in T cells. In this study we investigated the effects of VIP and PACAP on FasL expression and subsequent direct and bystander lysis by CD4(+) effectors generated in vivo. VIP/PACAP inhibit FasL expression in allogeneic effectors, and reduce

Fas-mediated cytotoxicity against specific allotargets and syngeneic bystanders. VIP/PACAP also inhibit FasL expression in antigen-specific CD4(+) effectors, and reduce their cytotoxic activity against both the stimulatory *APC* , and syngeneic or allogeneic bystanders. Since bystander lysis is involved in the pathogenesis of several autoimmune and inflammatory diseases, the identification of regulatory factors that limit this process is highly significant.

4/3,AB/27
DIALOG(R)File 155:MEDLINE(R)

08984565 20275731 PMID: 10814792
Targeting antigen-specific T cells by genetically engineered antigen presenting cells. A strategy for specific immunotherapy of autoimmune disease.
Wu J M; Wu B; Guarnieri F; August J T; Drachman D B
Department of Neurology, Johns Hopkins School of Medicine, 5-119 Meyer Building, 600 N. Wolfe St., Baltimore, MD 21287-7519, USA. Journal of neuroimmunology (NETHERLANDS) Jul 1 2000, 106 (1-2) p145-53, ISSN 0165-5728 Journal Code: 8109498
Contract/Grant No.: 1R01NS37205; NS; NINDS; NS07368; NS; NINDS Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We describe a strategy for specific immunotherapy of autoimmune disease based on targeting the antigen-specific T cells in an experimental model of myasthenia gravis. To address the problem of heterogeneity of the T cell repertoire, we have genetically engineered antigen presenting cells (*APCs*) to process and present epitopes of the autoantigen, acetylcholine receptor (AChR), to the entire spectrum of AChR-specific syngeneic T cells. *APCs* derived from BALB/c mice were stably transfected with cDNA for the key immunogenic domain of the AChR alpha-subunit, flanked by sequences of the lysosome-associated membrane protein (LAMP) that direct *APCs* to process and present the antigen via the MHC Class II pathway. Transfected *APCs* strongly stimulated AChR-specific T cells from BALB/c mice. *Fas* *ligand*, or antibody to Fas, abrogated the T cell response, by inducing apoptosis of the *APC*-stimulated T cells. The new results of this investigation are (1) that autoreactive T cells can be effectively targeted by autologous *APCs* that are engineered to present the relevant autoantigen, and (2) that these specifically targeted and activated T cells can be profoundly inhibited by agents that trigger the Fas-mediated apoptosis pathway. The present findings suggest that engineering *APCs* for simultaneous presentation of the autoantigen and delivery of FasL will provide a powerful strategy for the elimination of autoreactive T cells.

4/3,AB/28
DIALOG(R)File 155:MEDLINE(R)

08953888 20243543 PMID: 10779747
The regulation of CD95 (*Fas*) *ligand* expression in primary T cells: induction of promoter activation in CD95LP-Luc transgenic mice.
Norian L A; Latinis K M; Eliason S L; Lyson K; Yang C; Ratliff T; Koretzky G A
Interdisciplinary Graduate Program in Immunology, Department of Internal Medicine, University of Iowa, Iowa City, IA 52242, USA.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) May 1 2000, 164 (9) p4471-80, ISSN 0022-1767 Journal Code: 2985117R
Contract/Grant No.: DK54014; DK; NIDDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The interaction between CD95 (Fas) and CD95L (*Fas* *ligand*) initiates apoptosis in a variety of cell types. Although the regulation of CD95L expression on activated T cells is an area of intense study, knowledge related to the induction of CD95L promoter activity in primary T cells is lacking. In this report we describe the generation of a novel transgenic mouse strain, CD95LP-Luc, in which murine CD95L promoter sequence controls the expression of a luciferase reporter gene. We use these mice to illustrate several important findings related to transcriptional regulation of CD95L in primary T cells. We demonstrate that maximal CD95L promoter activity occurs only after prolonged T cell stimulation and requires costimulation through CD28. We provide evidence that thymocytes express CD95L/luciferase after strong TCR ligation and that inducible CD95L promoter activation is present, but unequal, in both Th1 and Th2 effector cells. We also illustrate that while agonist peptide presentation by *APCs* generates robust proliferation during a primary T cell response, the same stimulus induces only modest CD95L promoter activity. These results suggest alternate explanations for the well-characterized delay in CD95-mediated activation-induced cell death following initial ligation of the TCR.

4/3,AB/29
DIALOG(R)File 155:MEDLINE(R)

08951973 20241576 PMID: 10780664
CD4+ T cell-mediated cytotoxicity toward thyrocytes: the importance of Fas/*Fas* *ligand* interaction inducing

apoptosis of thyrocytes and the inhibitory effect of thyroid-stimulating hormone.

Kawakami A; Matsuoka N; Tsuboi M; Koji T; Urayama S; Sera N; Hida A; Usa T; Kimura H; Yokoyama N; Nakashima T; Ishikawa N; Ito K; Kawabe Y; Eguchi K The First Department of Internal Medicine, Nagasaki University School of Medicine, Tokyo, Japan.

Laboratory investigation; a journal of technical methods and pathology (UNITED STATES) Apr 2000, 80 (4) p471-84, ISSN 0023-6837 Journal Code: 0376617

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The accumulation of activated CD4+ T cells and antigen (Ag)-dependent cellular interactions between thyrocytes and CD4+ T cells have been determined in thyroid gland from patients with Graves' disease. The Fas/ *Fas* *ligand* (FasL) interaction between antigen-presenting cells and T cells regulates the apoptosis of the former cells triggered by the latter cells. The inhibition of Fas-mediated apoptosis in thyrocytes could be a underlying mechanism of hyperplasia of thyrocytes in patients with Graves' disease. We investigated the potential role of Fas/FasL interaction between thyrocytes and CD4+ T cells in the induction of Fas-mediated apoptosis of the former cells induced by the latter cells. The presence of only a few specific T cells responsive to a putative autoantigen has hampered the investigation of specific T cell activation toward antigen-presenting cells (*APCs*). Therefore, we used a superantigen, staphylococcal enterotoxin B (SEB), to examine specific T cell activation toward thyrocytes in vitro since it stimulates a large proportion of T cells with particular Vbeta elements. Spontaneous apoptosis of thyrocytes in culture was not found even in the presence of various kinds of cytokines. In contrast, a clear induction of Fas-mediated apoptosis by anti-Fas IgM was determined in interferon-gamma (IFN-gamma)-stimulated thyrocytes. In addition, a significant cytotoxicity of purified CD4+ T cells toward IFN-gamma-stimulated thyrocytes in the presence of SEB was induced, and the addition of anti-HLA-DR and -DQ monoclonal antibodies (mAbs) or blockade of the Fas/FasL interaction reduced this cytotoxicity. FasL expression of CD4+ T cells cocultured with IFN-gamma-stimulated thyrocytes in the presence of SEB was clearly induced. Furthermore, the addition of mAbs against CD54 and CD58 inhibited both cytotoxicity and FasL expression of CD4+ T cells. The cytotoxicity of CD4+ T cells toward IFN-gamma-stimulated, SEB-pulsed thyrocytes was markedly inhibited when we used thyrocytes cultured with IFN-gamma in the presence of thyroid-stimulating hormone (TSH) as target cells. Our results suggest that 1) CD4+ T cells were activated by thyrocytes expressing MHC class II molecules in an SEB-dependent manner and then expressed FasL. 2) These activated FasL+ CD4+ T cells killed thyrocytes by interacting with Fas on thyrocytes and FasL on activated CD4+ T cells. The presence of costimulating molecules such as CD54 and CD58 on thyrocytes was also necessary to generate activated FasL+ CD4+ T cells. 3) Since the actions of thyroid stimulating antibody (TSAb) toward thyrocytes are similar to those of TSH, one goitrogenic activity of TSAb may, in part, be due to the inhibitory effect on Fas-mediated apoptosis of thyrocytes triggered by activated CD4+ T cells.

4/3,AB/30

DIALOG(R)File 155:MEDLINE(R)

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Antigen presenting cells expressing *Fas* *ligand* down-modulate chronic inflammatory disease in *Fas* *ligand*-deficient mice.

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Document type: Journal Article

Languages: ENGLISH

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We assessed the effect of modified antigen presenting cells (*APCs*) expressing high levels of *Fas* *ligand* (*APC* -FasL) on post-viral chronic inflammatory disease. FasL-deficient B6-gld/gld mice infected with murine cytomegalovirus (MCMV) cleared the virus from their lungs, kidneys, and livers within 2 weeks of infection. However, inflammation persisted in these organs for more than 8 weeks, with a chronically increased T-cell response to MCMV-infected *APCs* and production of autoantibodies. Administration of *APC*-AdFasL at 4 weeks suppressed this inflammation and diminished the T-cell response and autoantibody production. *APC* -AdFasL that had been transfected with ultraviolet-irradiated MCMV were more effective than uninfected *APC* -AdFasL in ameliorating the chronic inflammation. *APC*-AdFasL migrated preferentially to the spleen, where they triggered apoptosis of lymphocytes in the marginal zone of the spleen. These results confirm that Fas-mediated apoptosis is not required for clearance of virus, but is required for down-modulation of the virally induced chronic inflammatory response. This organwide effect of *APC*-AdFasL appears to be mediated by elimination of activated T lymphocytes in the spleen before their

emigration to the target organs.

4/3,AB/31
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08852469 20137287 PMID: 10674822
Fas/*Fas* *ligand*-mediated apoptosis of murine Langerhans cells. Kawamura T; Azuma M; Kayagaki N; Shimada S; Yagita H; Okumura K Department of Immunology, Juntendo University School of Medicine, Tokyo, Japan. kawamura@box-k.nih.gov
Journal of dermatological science (IRELAND) Feb 2000, 22 (2) p96-101 , ISSN 0923-1811 Journal Code: 9011485
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Epidermal Langerhans cells (LC) are potent antigen-presenting cells (*APC*), that play a crucial role in initiating cutaneous immune responses. The Fas/*Fas* *ligand* pathway has been implicated as an important cellular pathway in the regulation of peripheral immunity. The morphologic, functional and phenotypic characteristics of LC are becoming well-characterized. However, the mechanisms involved in eliminating LC are poorly understood. In this report, we demonstrated that murine epidermal LC constitutively express the Fas antigen (CD95) and the expression was up-regulated by the addition of IFN-gamma in cultures. Interestingly, epidermal LC underwent apoptosis by the addition of both recombinant soluble *Fas* *ligand* (FasL) and IFN-gamma, but not by FasL alone. These results suggest that LC may acquire the susceptibility to Fas-mediated apoptosis through up-regulation of the Fas expression by IFN-gamma derived from activated T cells and that the elimination of LC may be important for preventing excess cutaneous inflammatory diseases.

4/3,AB/32
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08741806 20021824 PMID: 10553053
Dendritic cells are resistant to apoptosis through the Fas (CD95/APO-1) pathway.
Ashany D; Savir A; Bhardwaj N; Elkon K B
Hospital for Special Surgery, Cornell University Medical Center, New York 10021, USA. ashanyd@hss.edu
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Nov 15 1999, 163 (10) p5303-11, ISSN 0022-1767 Journal Code: 2985117R
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Document type: Journal Article
Languages: ENGLISH
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Immunoregulation of lymphocytes and macrophages in the peripheral immune system is achieved in part by activation-induced cell death. Members of the TNF receptor family including Fas (CD95) are involved in the regulation of activation-induced cell death. To determine whether activation-induced cell death plays a role in regulation of dendritic cells (DCs), we examined interactions between Ag-presenting murine DCs and Ag-specific Th1 CD4+ T cells. Whereas mature bone marrow- or spleen-derived DCs expressed high levels of Fas, these DCs were relatively insensitive to Fas-mediated killing by the agonist mAb, Jo-2, as well as authentic *Fas* *ligand* expressed on the CD4+ T cell line, A.E7. The insensitivity to Fas-mediated apoptosis was not affected by priming with IFN-gamma and/or TNF-alpha or by blocking the DC survival signals TNF-related activation-induced cytokine and CD40L. However, apoptosis could be induced with C2-ceramide, suggesting that signals proximal to the generation of ceramide might mediate resistance to Fas. Analysis of protein expression of several anti-apoptotic mediators revealed that expression of the intracellular inhibitor of apoptosis Fas-associated death domain-like IL-1-converting enzyme-inhibitory protein was significantly higher in Fas-resistant DCs than in Fas-sensitive macrophages, suggesting a possible role for Fas-associated death domain-like IL-1-converting enzyme-inhibitory protein in DC resistance to Fas-mediated apoptosis. Our results demonstrate that murine DCs differ significantly from other *APC* populations in susceptibility to Fas-mediated apoptosis during cognate presentation of Ag. Because DCs are most notable for initiation of an immune response, resistance to apoptosis may contribute to this function.
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